Advances in Medicine, Psychology and Public Health (AMPPH)

Systematic Review in Clinical Medicine

Surfactant Protein-D (SP-D) serum levels as a predictor of COVID-19 severity and mortality: A systematic review and meta-analysis

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Abstract

Introduction: This study investigates the diagnostic and prognostic potential of Surfactant Protein D (SP-D), in distinguishing COVID-19 patients from healthy controls and predicting outcomes in infected individuals. Through a comprehensive systematic review and meta-analysis, we aim to elucidate the role of SP-D in the clinical management of COVID-19, addressing a crucial gap in current biomarker research.

Methods: We searched PubMed, Embase, Web of Science, and Scopus, for articles published in English up to January 21, 2024. We employed a systematic review and meta-analysis approach, searching multiple databases for studies that measured SP-D levels in COVID-19 patients and healthy controls. The inclusion criteria were strictly defined to ensure the selection of studies with high-quality data, and statistical analyses were performed to assess the diagnostic and prognostic value of SP-D in the context of COVID-19.

Results: Twelve studies were included in this systematic review and meta-analysis. Pooled analysis showed that SP-D levels among those groups of patients varied and amounted to 44.38±74.71 vs. 21.29±31.8, respectively (SMD = 1.39; 95%CI: 0.35 to 2.43; p=0.009). Pooled

analysis of SP-D values among severe and non-severe COVID-19 patients was 58.28±101.8 and 94.69±114.22 respectively (SMD = 0.44; 95%CI: -0.78 to 1.66; p=0.48). SP-D levels also did not detect statistically significant differences in COVID-19 patients who survived and died in the hospital (27.18±16.4 vs. 29.12±14.14; SMD = 0.07; 95%CI: -0.28 to 0.42; p=0.70).
Conclusions: Results of the current systematic review and meta-analysis indicated that SP-D may be a good marker for dif-ferentiating patients with COVID-19 from healthy patients, but it does not provide prognostic value among patients with COVID-19. Further studies are needed to confirm the results.

Take-home message: The systematic review and meta-analysis conducted on circulating pneumoproteins, specifically SP-D, in the context of COVID-19, suggests that SP-D can differentiate between COVID-19 patients and healthy individuals but lacks prognostic value for outcomes among those with COVID-19. This indicates a need for further research to explore and confirm the diagnostic capabilities of SP-D and other pneumoproteins in COVID-19.
Keywords: ARDS; COVID-19; meta-analysis; mortality; Surfactant Protein-D; severity.

INTRODUCTION

The search for diagnostic and prognostic biomarkers among patients diagnosed with COVID-19 is an important area of scientific research in the period since the outbreak of the pandemic. Efforts to find optimal diagnostic and prognostic biomarkers did not cease once the pandemic was under control [1]. Biomarkers are intended to facilitate the prediction and stratification of patients with COVID-19, i.e., to select populations with an increased risk, thus the likelihood of a more aggressive course of the disease, an increased chance of admission to hospital, the need for care in intensive care units, or indicate an increased risk of risk of death [2,3]. Due to the fact that in severe cases of COVID-19, an increased response of the immune system is observed, sometimes leading to a cytokine storm, many of the biomarkers are derived from indicators of inflammation, e.g. neutrophil count, neutrophil-to-lymphocyte ratio or C-reactive protein (CRP) [4 – 6]. Especially the latter, CRP, is extremely useful in distinguishing severe vs. non-severe course of COVID-19. A high CRP value allowed for the prediction of the risk of low oxygen saturation or an increased risk of hospitalisation. This family of biomarkers also includes interleukins, e.g. IL-6 [7 – 9]. Other groups of biomarkers may indicate potential multi-organ damage in the course of COVID-19, e.g. transaminases or lactate dehydrogenase (LDH) [10,11]. Another group of biomarkers are those that are supposed to indicate response to treatment, which is particularly important in the case of COVID-19, due to the fact that insufficient response to treatment should be noticed quickly and lead to modification of therapy, including intensification of current treatment [12,13].

Ke et al. defined pneumoproteins as lung-specific proteins released from the lungs as a result of tissue damage [14]. Some pneumoproteins are not only present on the surface of the respiratory system, but also penetrate the circulation and can be detected in the blood. Previously, pneumoproteins have been investigated for their usefulness as prognostic biomarkers in chronic obstructive pulmonary disease (e.g., surfactant protein-D, SP-D; club cell secretory protein-16, CC-16) [15,16]. Park et al. showed that a reduction in CC-16 concentration in COPD patients was associated with an accelerated reduction in the respiratory fraction FEV1 over a 9-year period [17]. Moreover, Lomas et al. showed that the mean level of SP-D was increased in the population of COPD patients compared to current smokers and people who smoked in the past; in both comparison groups, no airflow obstruction was identified [18]. However, further research is required to assess the usefulness

of pneumoproteins in selected patient populations. This need is indicated, among others, by: study conducted by Jeon et al. among HIV-infected individuals [15]. Due to the fact that lung damage occurs in the course of COVID-19, pneumoproteins can potentially be used as diagnostic and prognostic biomarkers, as indicated by preliminary studies. In addition to the pneumoproteins mentioned above, important from the point of view of potential prognostic and diagnostic properties in the course of COVID-19 are: Krebs von den Lungen-6 (KL-6), surface protein A (SP-A) and advanced glycation end-products (RAGEs) [14].

Taking into consideration all, the aim of the current study is to conduct systematic review and meta-analysis of circulating in blood pneumoproteins in the context of their usefulness as prognostic and diagnostic biomarkers in COVID-19 on the example of SP-D.

METHODS

A systematic review was conducted using the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [19]. The study was preregistered in the International Prospective Register of Systematic Review (PROSPERO) with the registration number CRD42024510643.

Data sources and search strategy

Two independent reviewers (K.D. and M.P.) conducted a thorough screening of all records identified in the initial search. The screening process involved evaluating the relevance of the records based on their titles, abstracts, and full texts. Conflicts between the two reviewers were resolved by discussion among all the authors. We searched PubMed, Embase, Web of Science, and Scopus, for articles published in English from January 01, 2020, until January 21, 2024. Search in the aforementioned databases, we employed combinations of Medical Subject Heading: "Pulmonary Surfactant Associated Protein D" OR "surfactant protein D" OR „SP-D" AND "coronavirus" OR "corona-virus" OR "COVID" OR "COVID 19" OR "COVID-19" OR "COVID19" OR "Coronavirus disease 2019" OR "nCOV" OR "novel coronavirus" OR "new coronavirus" OR "2019-nCoV" OR "SARS-CoV2" OR "Sars-CoV-2 infection" OR "severe-acute-respiratory-syndrome-related coronavirus 2".

Following the elimination of duplicates, two autonomous researchers (K.D. and M.T.) examined the titles and abstracts of the acquired papers to find articles that satisfied the inclusion criteria. Subsequently, the complete text of the chosen articles was obtained and assessed. In the event of divergent opinions, a consensus was formed or a third researcher (KA) was consulted to make a decision. Every article obtained was compared to prevent any possible duplication. In addition, the reference lists of the collected publications and relevant reviews were manually examined to identify any other potential articles.

Inclusion criteria and study eligibility

Trials were considered eligible for analysis if they met the following criteria: (1) reported quantitative measures of plasma SP-D in individuals with the COVID-19 and in healthy controls, severe vs. non-severe COVID-19 patients as well as survive vs. non-survive COVID-19 patients; (2) reported original data; and (3) were not case reports due to low sample size. We excluded duplicated studies or multiple publications of the same study. We also excluded basic research, review articles, conference papers, editorials, case reports, non-human research studies, incorrect subject studies, non-English studies and studies of unavailable data.

Data extraction

For each eligible article, 2 reviewers (K.D. and G.N.) independently extracted data using a standard data collection sheet, which included demographic information about study participants, methodological information (e.g., first author name, origin country, study design), and information about SP-D levels. Discussions with the third researcher (KA) helped to resolve any disagreements. Corresponding authors of select studies were contacted in cases of missing data.

Quality assessment

Two researchers (K.D. and M.T.) independently rated risk of bias using the Newcastle-Ottawa quality assessment scale [20]. Different opinion in the eligibility and quality assessment of the records were resolved by discussion with the senior investigator (L.S.). For case-control studies, this comprised the determination of (1) adequate case definition, (2) representativeness of cases, (3) selection of control, (4) definition of control, (5) comparability of case and control groups, (6) exposure, (7) whether there were identical exposure methods for cases and controls, and (8) nonresponse rate. We used the conventional cut-off values to code a NOS ≥7 as high, 5-6 as moderate and 4 as low-quality studies.

Statistical analysis

The statistical analysis was performed in accordance with the recommendations of the Cochrane Collaboration and the standards for reporting the quality of meta-analyses [21]. All statistical analyses were two-sided, with statistical significance attained by a P-value <0.05. The mean and standard deviation (SD) of all parameters were extracted from the included articles for continuous and binary data. When the continuous outcome was reported as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [22]. A random-effects meta-analysis model based on inverse-variance approach in RevMan software (version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, Denmark) was used to pool the data. Standardized mean differences (SMDs) in the form of Hedges' g (and 95% Confidence Intervals [CIs]) were used to calculate the difference between the levels. The Q value and I^2 were used to test the heterogeneity. P < 0.10 was considered to indicate heterogeneity between combined studies. I^2 values of 0–25% indicated no heterogeneity, 25–50% indicated mild heterogeneity, 50–75% indicated moderate heterogeneity, and 75–100% indicated major heterogeneity [23]. In case of more than 10 studies were combined in the meta-analysis, a funnel plot would be used to assess the publication bias by Egger's test. Funnel plots were visually inspected for potential outliers which were analyzed using the leave-one-out meta-analysis method in STATA 17.0. All analyses were based on previous published studies; thus no ethical approval and patient consent were required.

RESULTS

Study selection and characteristics of the included studies

A total of 916 records were found from the literature and two more were identified from references of included articles. After duplicate removal, another 372 were considered irrelevant and excluded from further analysis following abstract and title review, leaving 35 studies for full-text review. Further, 23 studies were excluded from analysis for not reporting plasma SP-D levels. A total of 12 publications met all inclusion criteria and were included in the meta-analysis [24 – 35]. The data used for the present analysis are derived from a total of 892 subjects. The participants were postmenopausal women from China, Germany, Indonesia, Japan, Turkey, Republic of Korea and Russia. A detailed description of all meta-analyzed studies can be found in Tables 1. Detailed NOS scores are presented in the Table 1 for all 12 studies that were meta-analyzed. Upon performing quality assessments for these studies, all studies were of high quality.

Findings from the meta-analysis

Five studies reported SP-D levels among COVID-19 patients and control group. Pooled analysis showed that SP-D levels among those groups of patients varied and amounted to 44.38±74.71 vs. 21.29±31.8, respectively (SMD = 1.39; 95%CI: 0.35 to 2.43; p=0.009; Figure 2).

Pooled analysis of SP-D values among severe and non-severe COVID-19 patients was 58.28±101.8 and 94.69±114.22 respectively (SMD = 0.44; 95%CI: -0.78 to 1.66; p=0.48). SP-D levels also did not detect statistically significant differences in COVID-19 patients who survived and died in the hospital (27.18±16.4 vs. 29.12±14.14; SMD = 0.07; 95%CI: -0.28 to 0.42; p=0.70).

Figure 1. PRISMA checklist.

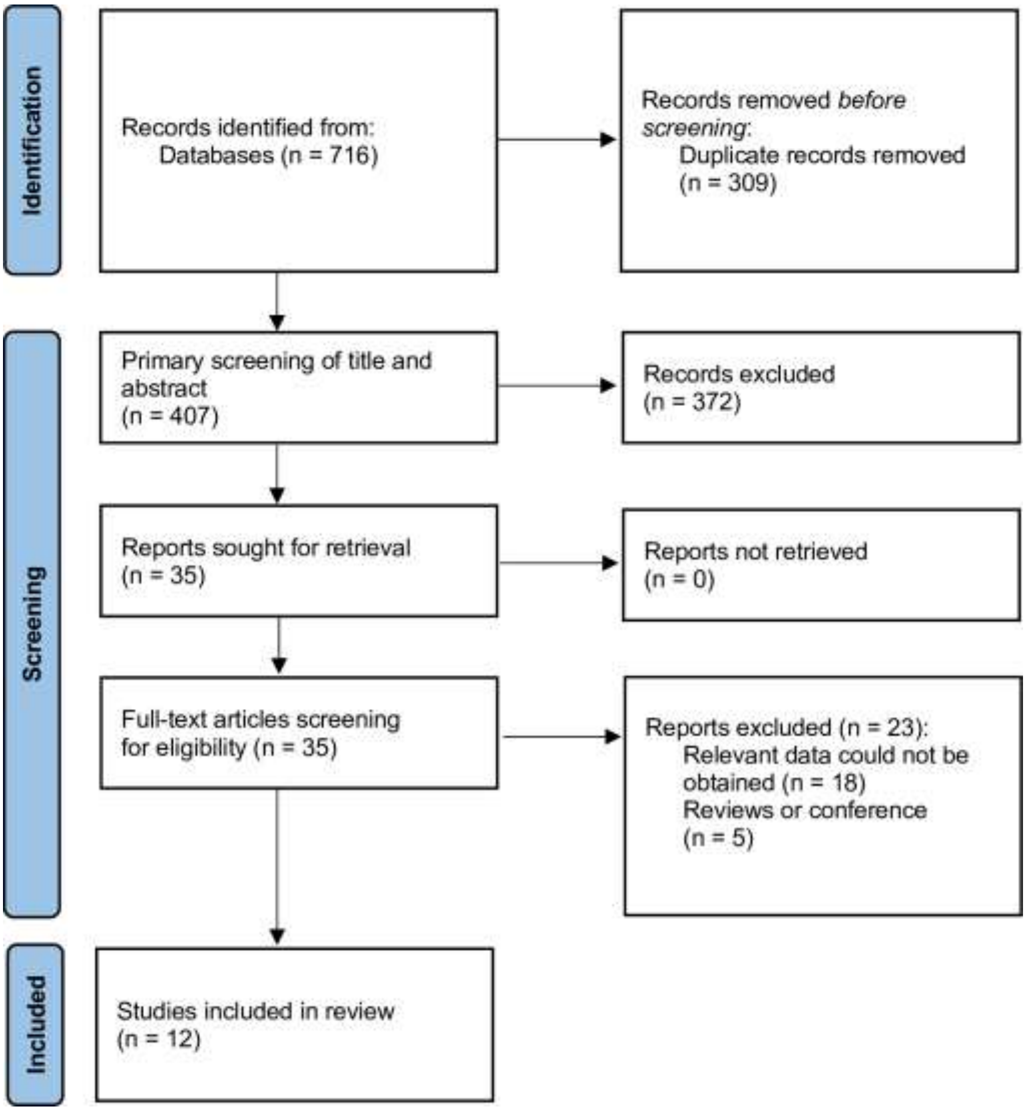


Table 1. Baseline characteristics of included trials.

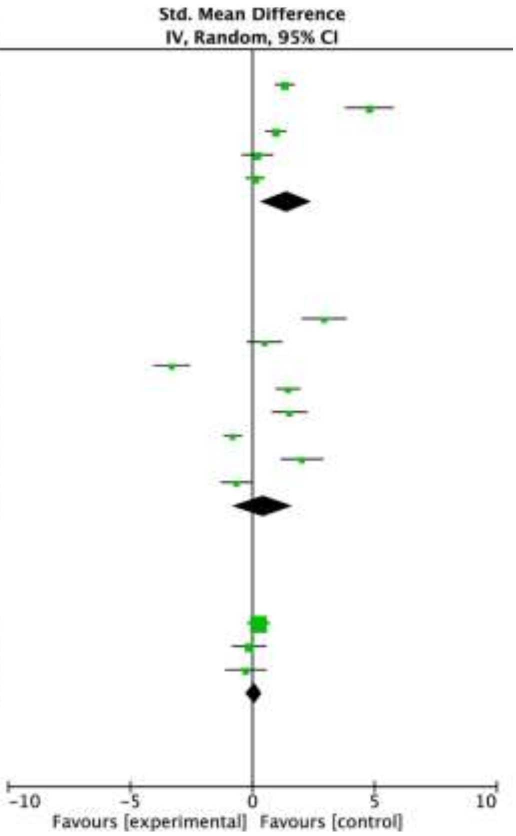
Study	Country	Study design	Study group	No. of patients	Age	Sex, male	BMI	NOS score
Agustama et al., 2022	Indonesia	PS	Survivors	39	55.56±12.96	25 (64.1)	26.4±1.6	8
			Non-survivors	37	49.43±10.29	21 (56.8)	25.7±1.3	
Alay et al., 2021	Turkey	PS	COVID-19	64	55.17 ± 16.1	29 (45.3)	NS	7
			Control	50	NS	21 (42.0)	NS	
Arakawa et al., 2022	Japan	RS	Severe	12	54.75±10.96	9	NS	7
			Non-severe	12	50.75±15.88	7	NS	
Fukuda et al., 2021	Japan	PS	Severe	22	61.93±3.08	18	24.7±1.6	8
			Non-severe	50	41.93±7.08	30	23.0±1.9	

Herr et al., 2021	Germany	PS	COVID-19	35	63.86±3.18	26	27.08±1.31	8
			Control	28	62.42±2.14	28 (100)	26.3±0.99	
			Survivors	24	NS	NS	NS	
			Non-survivors	11	NS	NS	NS	
Karasi et al., 2022	Turkey	PS	COVID-19	80	50.6 ± 2.2	37	NS	8
			Control	30	50.3 ± 1.4	14	NS	
			Severe	50	50.8 ± 2.5	21	NS	
			Non-severe	30	50.8 ± 2.5	16	NS	
Khadzhieva et al., 2021	Russia	RS	Survivors	90	46.6 ± 2.5	49 (58.3%)	30.8 ± 1.4	8
			Non-survivors	19	62.8 ± 3.8	11 (61.1%)	29.1 ± 1.4	
Kim et al., 2021	Republic of Korea	PS	COVID-19	31	NS	NS	NS	8
			Control	13	NS	NS	NS	
Saito et al., 2020	Japan	PS	Severe	12	65.1 ± 10.7	7	24.5 ± 4.2	9
			Non-severe	34	49.6 ± 15.7	14	23.0 ± 4.1	
Takenaka et al., 2023	Japan	RS	Severe	89	51.6 ± 4.3	49	NS	8
			Non-severe	42	43.3 ± 5.9	20	NS	
Tong et al., 2021	China	PS	Severe	9	57.5 ± 8.1	4	NS	8
			Non-severe	30	44.5 ± 7.5	16	NS	
Wang et al., 2021	China	RS	Severe	12	55.7 ± 5.1	9	NS	8
			Non-severe	52	41.7 ± 5.2	26 (50.0%)	NS	

Note: BMI = body mass index; NOS = Newcastle Ottawa scale; PS = prospective study; RS = retrospective study

Figure 2. Forest plot of SP-D levels among (A) COVID-19 and non-COVID-19 patients; (B) severe and non-severe COVID-19 patients; (C) survivors and non-survivors COVID-19 patients. The center of each square represents the stanarized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.1.1 COVID-19 vs. control								
Alay 2021	28.48	23.88	64	4.6	1.8	50	20.8%	1.32 [0.91, 1.73]
Herr 2021	34.19	4.73	35	15.71	2.16	28	17.9%	4.79 [3.79, 5.78]
Karslı 2022	6.19	3.46	80	3.28	1.29	30	20.7%	0.95 [0.51, 1.39]
Kim 2021	6.57	1.93	31	6.23	0.6	13	19.8%	0.20 [-0.45, 0.85]
Takenaka 2023	87.15	105.23	131	77	30.92	31	20.8%	0.11 [-0.29, 0.50]
Subtotal (95% CI)			**341**			**152**	**100.0%**	**1.39 [0.35, 2.43]**
Heterogeneity: Tau² = 1.30; Chi² = 82.90, df = 4 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.63 (P = 0.009)								
1.1.2 Severe vs. non-severe								
Alay 2021	60	12.9	18	28.9	7.8	22	12.2%	2.93 [2.01, 3.85]
Arakawa 2022	79.69	86.56	19	44.38	21.02	12	12.5%	0.50 [-0.24, 1.23]
Fukuda 2021	37.13	9.83	50	115.58	40.08	22	12.4%	-3.31 [-4.06, -2.56]
Karslı 2022	7.74	3.37	50	3.6	1.53	30	12.8%	1.45 [0.94, 1.96]
Saito 2020	237	210	12	61.9	50.7	34	12.5%	1.51 [0.78, 2.25]
Takenaka 2023	61.41	54.54	89	141.7	155.7	42	12.9%	-0.81 [-1.19, -0.43]
Tong 2021	449.7	125.8	9	245.9	90	30	12.2%	2.02 [1.14, 2.90]
Wang 2021	4.46	1.29	52	5.55	2.65	12	12.6%	-0.67 [-1.30, -0.03]
Subtotal (95% CI)			**299**			**204**	**100.0%**	**0.44 [-0.78, 1.66]**
Heterogeneity: Tau² = 2.96; Chi² = 204.25, df = 7 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.1.3 Survivors vs. non-survivors								
Agustama 2022	34.79	15.05	39	31.28	12.55	37	59.4%	0.25 [-0.20, 0.70]
Herr 2021	34.64	5.29	24	35.67	10.33	11	23.8%	-0.14 [-0.85, 0.57]
Khadzhieva 2021	6.48	2.78	23	7.38	4.27	7	16.8%	-0.28 [-1.13, 0.57]
Subtotal (95% CI)			**86**			**55**	**100.0%**	**0.07 [-0.28, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.39 (P = 0.70)								



DISCUSSION

Research conducted so far indicates an ambiguous role of pneumoproteins as prognostic and diagnostic biomarkers in the course of COVID-19. A meta-analysis conducted by Ke et al. showed that the SP-D level is higher among COVID-19 patients compared to healthy individuals. Moreover, the level of SP-D is lower among patients with mild to moderate COVID-19 compared to patients with severe disease. The above-mentioned meta-analysis identified a number of limitations, including: limited number of studies performed, lack of geographical representativeness or insufficient information regarding fluctuations in the level of pneumoproteins (including SP-D) depending on the time of measurement, e.g., so there is no sufficient information how the level changes between admission to hospital vs. levels in the subsequent days of hospitalization. These limitations remain in place [14].

As already mentioned, severe COVID-19 may be associated with significant damage to the endothelium in the lungs. Reducing endothelial damage, either due to a less severe course of the disease or by improving health, is associated with a reduction in pneumoproteins, including SP-D. Hence, the results of the mentioned meta-analysis seem to be biologically valid since the level of SP-D was higher in COVID-19 patients compared to healthy controls and statistically increases among patients with severe COVID-19 [24]. An important limitation of SP-D is the fact that in many chronic diseases, such as COPD, the level of SP-D is increased before the onset of COVID-19, which is due to chronic damage to the endothelium

in the respiratory system as the consequence of chronic illness. As a result of the course of COVID-19, this value increases, but chronic disease may be a confounding factor in studies. We cannot underestimate this risk of bias due to the fact that a more severe course of COVID-19 is observed among patients with chronic diseases [36]. In the context of COVID-19 usefulness, Choreño-Parra et al. conclude that SP-D is a significantly better prognostic biomarker for pandemic influenza than COVID-19 [37]. On the other hand, Togashi et al. showed that both KL-6 and SP-D enable the differentiation of patients with pneumonia resulting from COVID-19 infection (COVID-19 pneumonia) from COVID-19 pneumonia-like diseases. This distinction at an early stage of the therapeutic process may be crucial to the success of treatment [38].

SP-D has been studied widely as a potential diagnostic and prognostic biomarker in respiratory diseases. A meta-analysis conducted by Wang et al., which included 17 studies and 4639 patients, showed that the level of SP-D is increased in patients with COPD compared to healthy individuals. Additionally, during COPD exacerbation, increased SP-D levels were observed compared to patients with a stable clinical picture [39]. More difficulties has been observed in assessing the usefulness of SP-D as a prognostic and diagnostic biomarker in Idiopathic pulmonary fibrosis (IPF). A meta-analysis performed by Wang et al. showed a lack of statistical significance between the level of SP-D in patients with IPF compared to patients with non-IPF interstitial lung disease (ILD), which significantly limits the usefulness of the biomarker. However, in the mentioned meta-analysis, it was shown that the level of SP-D is statistically higher in patients with IPF compared to patients with lung infection or healthy controls. Furthermore, SPD has been shown to have some prognostic properties, more precisely higher levels of SPD correlated with an increased risk of death [40].

In turn, other studies indicate that in the case of some diseases (connective tissue disease), other pneumoproteins have a greater diagnostic potential than SP-D, e.g. KL-6 (Krebs von den Lungen-6) [41,42]. The latter biomarker, KL-6, appears to be particularly useful in identifying patients with severe lung injury in the course of COVID-19 [43]. The potential usefulness of the SP-D biomarker is very broad, and in addition to those mentioned above, it includes, among others: assessment of the efficiency of preoperative pulmonary rehabilitation in patients with lung cancer [44], early diagnosis of radiation pneumonitis [45] or assessment of lung injury after coronary artery bypass surgery [46].

The main problem when assessing the usefulness of a biomarker in clinical practice is determining the so-called cut-off. In the case of SP-D, a diagnostic cut off was proposed for the severity of Acute respiratory distress syndrome in the course of COVID-19 at the level of 44.24 ng/mL with a sensitivity of 92.3% and specificity of 94.1% [47].

Attention should be paid to the limitations of this meta-analysis. A relatively small number of studies that met the inclusion and exclusion criteria were included. A rigorous approach helps maintain internal validity. Additionally, a small amount of research has specifically targeted SP-D; SP-D was often one of many biomarkers measured without being the main purpose of the study. The studies were also characterized by high heterogeneity in design, e.g. the comparison group was sometimes based on patients with another disease of the respiratory system, and sometimes on healthy controls. There is also a lack of randomized trials designed to prospectively evaluate the prognostic properties.

CONCLUSIONS

Results of the current systematic review and meta-analysis indicated that SP-D may be a good marker for differentiating patients with COVID-19 from healthy patients, but it does not provide prognostic value among patients with COVID-19. Further studies are needed to confirm the results.

Author Contributions: Conceptualization: K.D.; methodology: K.D. and L.S; software: L.S.; validation: K.D.; formal analysis, K.D. and L.S.; investigation: K.D., M.T., M.P., G.N., D.S. and L.S.; resources: K.D. and L.S.; data curation: K.D.; writing—original draft preparation: K.D.; writing—review

and editing, K.D., M.T., M.P., G.N., D.S., M.K., A.R. and L.S.; visualization: K.D.; supervision: L.S. and K.D.; project administration: K.D.. All authors have read and agreed to the published version of the manuscript.

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